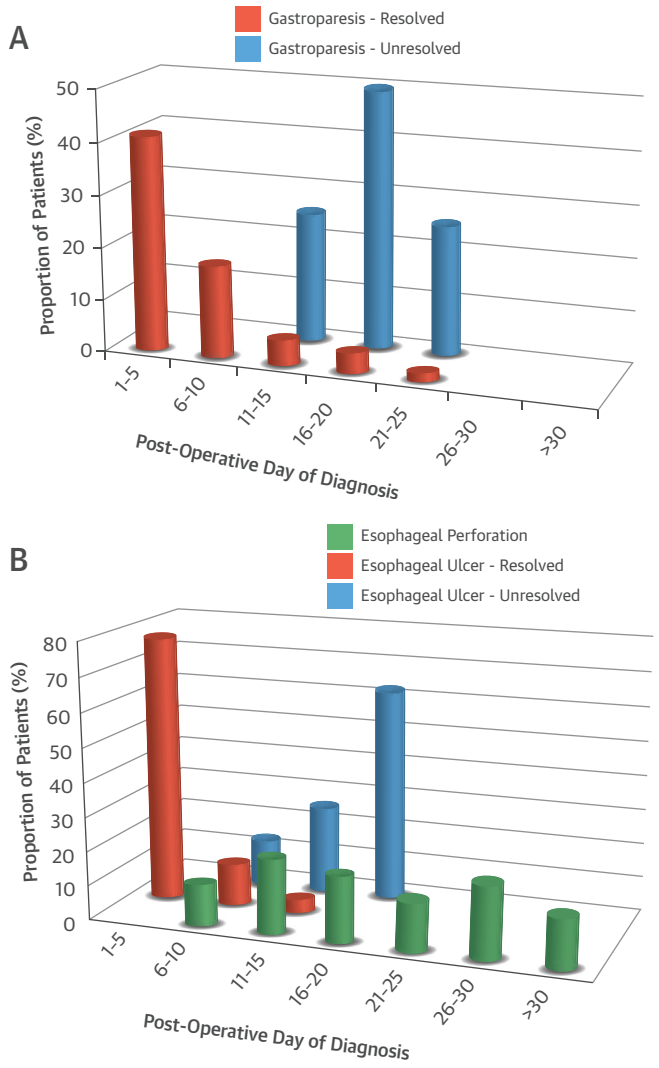
FIGURE 1 Time Course of Gastroesophageal Injury After Atrial Fibrillation Ablation



(A) Time course of gastroparesis diagnosis stratified by patients with spontaneous resolution of symptoms (n = 59, **red**) and patients whose symptoms remain unresolved (n = 4, **blue**). **(B)** Time course of esophageal injury diagnosis stratified by patients with spontaneous resolution of ulcer symptoms (n = 37, **red**), patients whose ulcer symptoms did not resolve spontaneously but did not have esophageal perforation (n = 14, **blue**), and patients in whom esophageal perforation developed (n = 31, **green**).

study, it is impossible to determine causation versus correlation.

We observed a bimodal temporal distribution of gastroesophageal injury after AF ablation, and all gastroparesis and esophageal injury diagnosed in the first 5 days after ablation resolved spontaneously. Symptom onset of gastric and esophageal injury more than 5 days after AF ablation is concerning for more severe injury. Our data reinforce the importance of close postoperative follow-up after AF ablation, even if patients do not report symptoms in the first few days after ablation of the posterior LA wall.

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Blunted Cardiomyocyte Remodeling Response in Exercise-Resistant Rats

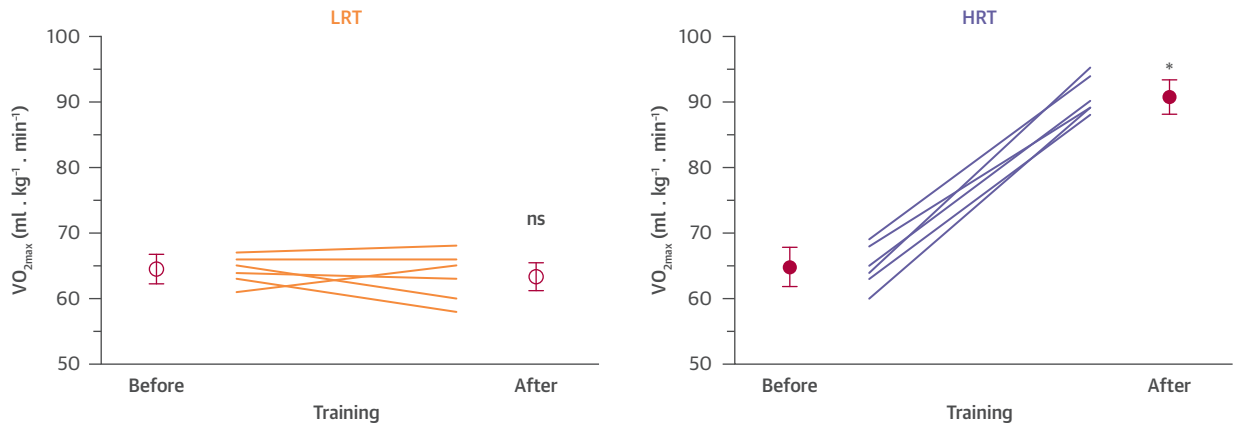
Increasing a subject's aerobic exercise capacity with training decreases cardiovascular morbidity and mortality. Of major concern is the key observation that

up to 20% of subjects demonstrate little or no change in maximal oxygen consumption (VO_{2max}) with exercise training (1) and can be considered exercise resistant. Our goal with the current research was to test the hypothesis that variation in training response is associated with cardiomyocyte functional response to training.

Exercise capacity can be divided into 2 components: an innate capacity operating in the untrained state, followed by an adaptive capacity acquired in response to exercise training. Previously, we developed rat models of low and high innate exercise capacity via 2-way artificial selective breeding and showed that high-intensity aerobic interval training improved VO_{2max} by increasing cardiomyocyte function in female rats with low innate exercise capacity (2). To improve our understanding of adaptive exercise capacity, we developed a second contrasting rat model system of high response trainers (HRT) and low response trainers (LRT); gain in maximal treadmill running distance with endurance training was used as the selection criterion. After 7 generations of selection (n = 1,371), HRT could improve running distance by 46% with training, whereas the LRT change was equivalent to a 2% loss in capacity; an estimated 10% of the variation in training response was caused by genotypic variance (3). Critical to this second model system, LRT and HRT demonstrated similar innate running capacities and body weights. In the current study, we compared cardiomyocytes isolated from the left ventricle of LRT and HRT female rats in the sedentary condition and in rats trained (TR) for 8 weeks using a high-intensity aerobic interval training protocol proven superior for increasing VO_{2max} and cardiac function in rats with low exercise tolerance (2).

HRT and LRT did not differ in VO_{2max} before training. After training, HRT rats demonstrated a 40% increase in VO_{2max}, whereas it remained unchanged in LRT rats (**Figure 1**). Cardiomyocytes from the left ventricle were isolated and prepared for confocal microscopy for dynamic cell measurements and stimulated at 7 Hz. In the sedentary condition, left ventricular (LV) cardiomyocytes from the HRT, relative to the LRT, were both significantly longer and narrower; these dimensional differences resulted in a higher length-to-width ratio and a lower calculated LV cell volume. Training resulted in no adaptive changes in LV cell width or width-to-length ratio, and maladaptive decreases in LV cell length and cell volume, in the LRT rats. In contrast, training uniformly produced positive adaptive morphometric increases in LV cardiomyocyte length, width, and volume in the HRT rats (p value for interaction of sedentary-TR difference between LRT and HRT <0.05; morphometric data not shown). In line with VO_{2max}, contractility did not differ between LRT and HRT in the sedentary condition but differed in the TR condition. HRT-TR demonstrated a 30% increase in fractional shortening, an 18% increase in speed of shortening, and a 12% increase in relengthening in LV cardiomyocytes, whereas no such increases occurred in LRT-TR. In addition, 4 measures of intracellular

FIGURE 1 LRT Rats Fail to Demonstrate Gains in Exercise Capacity in Response to Exercise Training Compared With HRT Rats



Maximal oxygen consumption (VO_{2max}) measured before and after 8 weeks of high-intensity aerobic interval training in low response trainers [LRT] and high response trainers [HRT] ($p < 0.001$).

calcium ion (Ca^{2+}) cycling demonstrated a similar pattern to contractility for: 1) twitch-stimulated Ca^{2+} amplitude; 2) sarcoplasmic reticulum Ca^{2+} load measured as caffeine-stimulated Ca^{2+} amplitude; 3) rate of Ca^{2+} release measured as time to peak Ca^{2+} transient; and 4) rate of diastolic Ca^{2+} removal measured as time to Ca^{2+} transient decay (p value for interaction of sedentary-TR difference between LRT and HRT: twitch- and caffeine-induced Ca^{2+} amplitude <0.001; time to 50% Ca^{2+} peak <0.05; and Ca^{2+} decay <0.01; data not shown).

A microarray experiment of the LV free wall identified 360 differentially expressed genes (DEGs) between HRT-sedentary relative to LRT-sedentary and 324 DEGs between HRT-TR relative to LRT-TR (the National Center for Biotechnology Information's Gene Expression Omnibus accession number GSE20997; UniGene identifiers were available for ~30% of Applied Biosystems 1700 Rat Genome Survey chip version 1.0 [updated probe annotation]). Of those, osteoglycin, an extracellular matrix protein, ranked as the greatest DEG, and was decreased in HRT relative to LRT in both the sedentary and TR conditions (-2.3 and -4.6 fold, respectively). We also performed a high-throughput functional annotation analysis (using the DAVID database) to identify enriched biological themes among the DEGs. In the sedentary condition, a gene set involving 5% of the DEGs were mapped to 3 serine-related activity terms that were enriched 5-fold in HRT relative to LRT. Among these, the gene with the greatest differential (3-fold higher in HRT relative to LRT) was kallikrein-related peptidase 12, a serine protease predicted to be a strong effector of cell growth and response. In the TR condition, 7% to 12% of the DEGs formed gene sets that were identified with terms pertaining to cell adhesion. Genes up-regulated in HRT included the cadherin-associated protein catenin and members of the integrin and metalloproteinase-disintegrin families; all are critically important in regulating angiogenesis, neurogenesis, and tissue development.

By developing a contrasting rat model system via artificial selection, we report the following (at several levels of organization): 1) cardiomyocyte remodeling accompanies expansion of VO_{2max} in response to training; and 2) molecular phenotypes involving extracellular matrix genes for growth signaling and cell adhesion are a central feature underlying the variations in response to training (4,5).

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Cardiovascular Function and Exercise Capacity in Patients With Colorectal Cancer

Does Anticancer Therapy Matter?

We congratulate Cramer et al. (1) for their recent evaluation of factors associated with decreased exercise tolerance (i.e., peak Vo_2) in a cross-sectional cohort of patients with colorectal cancer (CRC), heart failure, and healthy control subjects. As outlined in the accompanying editorial (2), this is a critical area of investigation that provides important information to characterize, monitor, and manage toxic effects across the cancer survivorship continuum. However, there are several notable limitations to the study, raising questions surrounding the validity of the central conclusion that "findings were evident independently of whether patients were undergoing chemotherapy."